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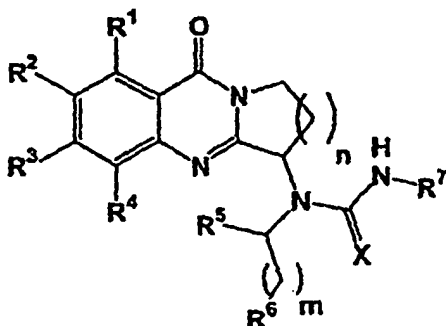
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(54) Title: 7,8,9,10-TETRAHYDRO-6H-AZEPINO, 6,7,8,9-TETRAHYDRO-PYRIDO AND 2,3-DIHYDRO-2H-PYRROLO[2,1-B]-QUINAZOLINONE DERIVATIVES



(I)

(57) Abstract: The invention relates to novel 7,8,9,10-tetrahydro-6H-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2H-pyrrolo[2,1-b]-quinazolinone derivatives of formula (I) and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor antagonists.

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5 7,8,9,10-Tetrahydro-6H-azepino, 6,7,8,9-tetrahydro-
 pyrido and 2,3-dihydro-2H-pyrrolo[2,1-b]-
 quinazolinone derivatives

10 The present invention relates to novel 7,8,9,10-tetrahydro-6H-azepino, 6,7,8,9-tetrahydro-
pyrido and 2,3-dihydro-2H-pyrrolo[2,1-b]-quinazolinone derivatives of the general
formula I and their use as pharmaceuticals. The invention also concerns related aspects
including processes for the preparation of the compounds, pharmaceutical compositions
containing one or more compounds of formula I, and especially their use as orexin
receptor antagonists.

15 The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the
orexin A (OX-A) (a 33 aminoacid peptide) and the orexin B (OX-B) (a 28 aminoacid
peptide) (Sakurai T. *et al.*, Cell, 1998, 92, 573-585). Orexins are found to stimulate food
consumption in rats suggesting a physiological role for these peptides as mediators in the
central feedback mechanism that regulates feeding behavior (Sakurai T. *et al.*, Cell, 1998,
20 92, 573-585). On the other hand, it was also proposed that orexins regulate states of sleep
and wakefulness opening potentially novel therapeutic approaches for narcoleptic patients
(Chemelli R.M. *et al.*, Cell, 1999, 98, 437-451). Two orexin receptors have been cloned
and characterized in mammals. They belong to the superfamily of G-protein coupled
receptor (Sakurai T. *et al.*, Cell, 1998, 92, 573-585): the orexin-1 receptor (OX₁) is
selective for OX-A and the orexin-2 receptor (OX₂) is capable to bind OX-A as well as
25 OX-B.

 . Orexin receptors are found in the mammalian host and may be responsible for
many biological functions such as pathologies including, but not limited to, depression;
anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive
neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual
30 dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression;
delerium; dementia; severe mental retardation and dyskinesias such as Huntington's
disease and Tourette syndrome; feeding disorders such as anorexia, bulimia, cachexia and
obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's
disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma;

hyperprolactinemia; hypopituitarism; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric dyskinesia; gastric ulcer; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to orexin.

The present invention provides 7,8,9,10-tetrahydro-6*H*-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2*H*-pyrrolo[2,1-*b*]-quinazolinone derivatives which are non-peptide antagonists of human orexin receptors. In particular, these compounds are of potential use in the treatment of obesity and/or sleep disorders.

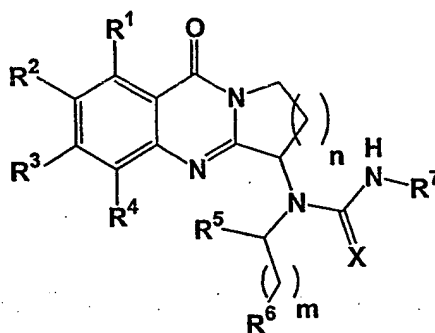
International Patent Applications WO99/09024, WO99/58533, WO00/47577, WO00/47580, disclose phenyl urea derivatives and WO00/47576, discloses quinolinyl cinnamide derivatives as orexin antagonists.

Furthermore, WO 0196302 has been published wherein piperidine derivatives as OX₁ and OX₂ antagonists are disclosed and WO 0185693 has been published wherein N-

acyltetrahydroisoquinoline derivatives as selective OX₂ antagonists are disclosed. In addition, WO 0244172 describes morpholine derivatives as antagonists of orexin receptors.

5 The novel compounds of the present invention belong to an entirely different class of low molecular weight compounds as compared to all prior art orexin receptor antagonists so far published.

10 The present invention relates to novel 7,8,9,10-tetrahydro-6H-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2H-pyrrolo[2,1-*b*]-quinazolinone derivatives of the general formula (I).



Formula (I)

15

wherein:

X is O or S;

n is the integer 1, 2, or 3;

20 m is the integer 0, 1, 2, 3;

R¹, R², R³, R⁴ independently represent cyano, nitro, halogen, hydrogen,

hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy,

heterocyclyl-lower alkyloxy, R⁸CO-, NR⁹R¹⁰CO-, R⁹R¹⁰N-, R⁸OOC-, R⁸SO₂NH-,

25 R¹¹-CO-NH- or R² and R³ together or R¹ and R² together or R³ and R⁴ together

may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom;

R⁵ represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

5 R⁶ represents hydrogen, lower alkyl, trifluoromethyl, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-CO_2H$, $-(CH_2)_m-CO_2$ -lower alkyl, $-(CH_2)_mCONH_2$, or $-(CH_2)_m-CONH$ -lower alkyl, or $-(CH_2)_m-CON$ -(lower alkyl)₂, or $-(CH_2)_m-N$ -(lower alkyl)₂;

R⁷ represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

10 R⁸ represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R⁹ and R¹⁰ independently represent hydrogen, alkyl, cycloalkyl, cycloalkyl-loweralkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R¹¹ represents alkyl, aryl, cycloalkyl, heterocyclyl, R⁹R¹⁰N- or R⁸O-.

The compounds of formula I can contain one or more asymmetric centres and can be
15 present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

20 In the present description the term "lower alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1-5 carbon atoms. Examples of straight-chain and branched C₁-C₈ alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isobutyl, tert-butyl, the isomeric pentylys, the
25 isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, tert-butyl and n-pentyl.

The term "lower alkenyl", alone or in combination, signifies a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, preferably allyl and vinyl.

30

The term "lower alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-

butoxy, preferably methoxy and ethoxy.

Lower alkenyloxy groups are preferably vinyloxy and allyloxy.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with
5 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms.

Examples of C₃-C₈ cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl and cyclooctyl, preferably cyclopropyl, cyclohexyl or lower alkyl substituted
cycloalkyl which may preferably be substituted with lower alkyl such as methyl-
cyclopropyl, dimethyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl, methyl-
10 cyclohexyl, dimethyl-cyclohexyl,

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group
which optionally carries one or more substituents, preferably one or two substituents,
each independently selected from cyano, halogen, hydroxy, lower alkyl, lower alkenyl,
lower alkoxy, lower alkenyloxy, nitro, trifluoromethyl, trifluoromethoxy, amino,
15 carboxy, alkoxycarbonyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-tert-
butoxyphenyl, 4-fluorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl and 2-
naphthyl. Preferred are carboxyphenyl, lower alkoxy-phenyl, hydroxyphenyl and
particularly phenyl.

20 The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl
group as previously defined in which one hydrogen atom has been replaced by an aryl
group as previously defined. Preferred are benzyl and benzyl substituted in the phenyl
ring with hydroxy, lower alkyl, lower alkoxy or halogen preferably fluorine.
Particularly preferred is benzyl.

25 For the term "heterocyclyl" and "heterocyclyl-lower alkyl", the heterocyclyl
group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may
be saturated, partially unsaturated or aromatic containing for example 1, 2 or 3
heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or
30 different. Example of such heterocyclyl groups are pyrrolidinyl, piperidinyl,
piperazinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl,
isoquinolyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl,
indazolyl, indolyl, isoindolyl, isoxazolyl, oxazolyl, quinoxalinyl, phthalazinyl,
cinnolinyl, dihydropyrrolyl, pyrrolidinyl, isobenzofuranyl, tetrahydrofuranyl,

dihydropyranyl. The heterocyclyl group may have up to 5, preferably 1, 2 or 3 optional substituents. Examples of suitable substituents include halogen, lower alkyl, amino, nitro, cyano, hydroxy, lower alkoxy, carboxy and lower alkyloxy-carbonyls.

5

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably chlorine and fluorine and particularly fluorine.

10

The term "carboxy", alone or in combination, signifies a -COOH group.

Preferred compounds are compounds of the general formula I wherein n is the integer 1 or 2, m is the integer 0, 1 or 2, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ have the meaning given in the formula I above and X represents oxygen.

15 Examples of preferred compounds are:

1-(9-Oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

20

3-Biphenyl-2-yl-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-Naphthalen-1-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

25

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

30

3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

- 1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;
- 5 1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
- 3-Biphenyl-2-yl-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 10 3-(2-Ethyl-phenyl)-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(6-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 15 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;
- 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 20 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
- 25 3-Biphenyl-2-yl-1-(7-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 30 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

- 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;
- 3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 5 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 3-Biphenyl-2-yl-1-(6,7-difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-
- 10 (2-trifluoromethoxy-phenyl)-urea;
- 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 15 3-Biphenyl-2-yl-1-butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;
- 1-Butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-*n*-propyl-phenyl)-urea;
- 1-Benzyl-3-biphenyl-2-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;
- 1-Benzyl-3-(2-ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-
- 20 urea;
- 1-Benzyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-*n*-propyl-phenyl)-urea;
- 3-Biphenyl-2-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 25 1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 3-(2-Ethyl-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 3-(2-Ethoxy-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-
- 30 phenyl-ethyl)-urea;
- 3-Naphthalen-1-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

- 3-Biphenyl-2-yl-1-(2,3-difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
 1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
 5 1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
 1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea;
 3-Biphenyl-2-yl-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-
 10 1-(1-phenyl-ethyl)-urea;
 1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
 3-(2-Ethoxy-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
 15 3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
 1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
 3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
 20 1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
 3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
 25 3-Biphenyl-2-yl-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
 1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea.
- 30 Especially preferred compounds are compounds of the general formula I wherein *n* is the integer 1 or 2, *m* is the integer 0, *R*⁵ represents methyl, *R*⁶ represents phenyl, *R*¹, *R*², *R*³, *R*⁴, and *R*⁷ have the meaning given in the formula I above and *X* represents oxygen.

Examples of especially preferred compounds are:

3-Biphenyl-2-yl-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

5 3-(2-Ethyl-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

10 3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

15 3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;

20 1-(6-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;

25 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;

30 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

- 3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 5 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 10 3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 15 1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea;
- 1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 20 3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 25 1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((*S*)-1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 3-Biphenyl-2-yl-1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((*S*)-1-phenyl-ethyl)-urea;
- 1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((*S*)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
- 30 1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((*S*)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea;

5 3-Biphenyl-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea.

Examples of physiologically usable or pharmaceutically acceptable salts of the
10 compounds of formula (I) are salts with physiologically compatible mineral acids such as hydrochloric acid, sulphuric or phosphoric acid; or with organic acids such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula (I) with free acidic groups can also form salts with physiologically compatible bases.

15 Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammonium salts such as Na, K, Ca or tetraalkylammonium salt. The compounds of formula (I) can also be present in the form of a zwitterion.

20 The compounds of formula (I) can contain several asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates and the meso-forms.

25 Preferred compounds as described above have IC_{50} values below 500 nM; especially preferred compounds have IC_{50} values below 100 nM which have been determined with the FLIPR (Fluorometric Imaging Plates Reader) method described in the beginning of the experimental section.

30 The compounds of the general formula (I) and their pharmaceutically usable salts can be used for the treatment of diseases or disorders where an antagonist of a

human orexin receptor is required such as obesity, diabetes, prolactinoma, cardiovascular disorders, cancer, pain, narcolepsy, sleep disorders like insomnia, sleep apnea, parasomnia, depression, anxiety, addictions, schizophrenia, neurodegenerative disorders and dementia.

5 The compounds of formula (I) and their pharmaceutically usable salts are particularly useful for the treatment of obesity and sleep disorders.

 The compounds of formula I may also be used in combination with one or more other therapeutically useful substances e.g. with other orexin receptor antagonists, with lipid
10 lowerer agents, with anorectic agents, with sleep inducing agents, with antidepressants or with other drugs beneficial for the prevention of treatment of obesity or sleep disorders.

 The compounds of formula (I) and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The
15 pharmaceutical preparations can be administered in enteral or oral form (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection
20 solutions).

 The compounds of formula (I) and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose,
25 corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules.

 Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

30

 Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

 Suitable adjuvants for injection solutions are, for example, water, alcohols,

polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

5

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

10

The invention also relates to processes for the preparation of compounds of Formula I.

15

The compounds of general formula (I) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7$ are as defined in formula (I) above. As the case may be any compound obtained with one or more optically active carbon atom may be resolved into pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates and the meso-forms in a manner known per se.

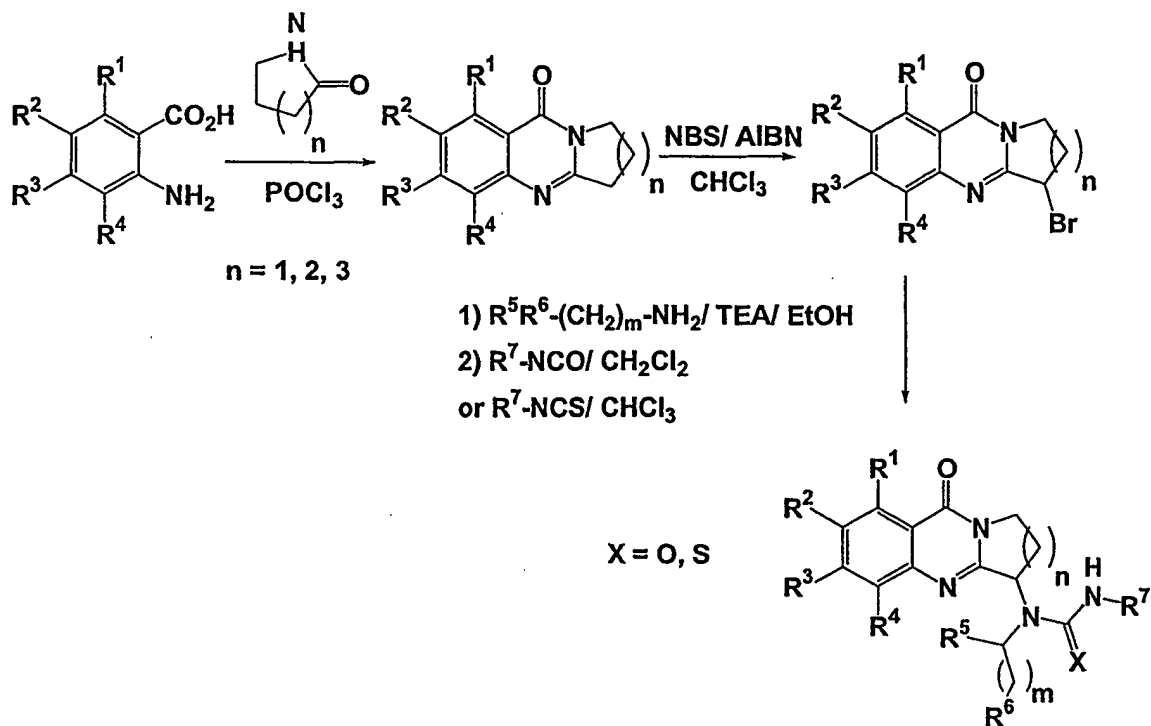
20

The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known per se.

25

30

The compounds of general formula (I) may be prepared from the corresponding 2-amino benzoic acid derivatives with the desired lactam by treatment with POCl_3 (Karimov A. *et al Chemistry of Natural Compounds* 1982, 18, 4, 466-472; Bhardwaj V. *et al Indian Journal of Heterocyclic Chemistry* 1999, 8, 173-176). Subsequent radical bromination (Kamal A. *et al J. Org. Chem.* 2001, 66, 997-1001) followed by substitution with the corresponding primary amine gave the secondary amine intermediate which is then converted to the desired urea or thiourea compound by reaction with commercially available or synthesized isocyanate or isothiocyanate (Scheme 1) (March J. *Advanced Organic Chemistry-Reactions, Mechanisms and Structure* 1992, page 418, 4th edition, John Wiley & Sons)

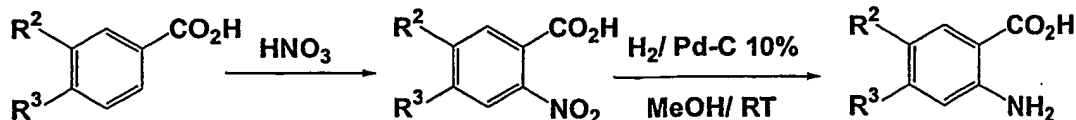


Scheme 1

5

2-Amino benzoic acid derivatives wherein R^1 and R^4 are hydrogen and which are not commercially available might be prepared from benzoic acid derivatives using standard procedures (Giencke A. *et al Liebigs Ann. Chem.* 1990, 569-579; Follope M.-P. *et al Eur. J. med. Chem.* 1992, 27, 291-295) as described in Scheme 2.

10

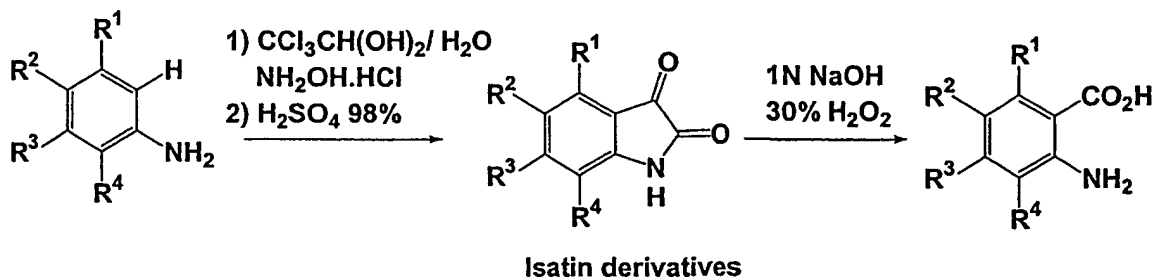


Scheme 2

15

Furthermore, 2-amino benzoic acid derivatives may also be prepared from aniline derivatives by reaction with chloral hydrate in the presence of hydroxylamine hydrochloride followed by acidic treatment yielding the isatin intermediate. This was converted to the

corresponding anthranilic acid derivative by reaction with hydrogen peroxide under basic conditions (Scheme 3) (Neal Bramson H. *et al J.Med.Chem.* 2001, 44, 4339-4358; Deady L.W. *et al J.Med.Chem.* 1997, 40, 2040-2046; Rowley M. *et al J.Med.Chem.* 1993, 36, 3386-3396; Hughes P. *et al J.Heterocyclic Chem.* 1990, 27, 2151-2163).



10
Scheme 3

20 Experimental Section

I. Biology

25 Determination of OX₁ and OX₂ receptor antagonistic activities

The OX₁ and OX₂ receptor antagonistic activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental method:

30 Intracellular calcium measurements

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor or the human orexin-2 receptor, were grown in culture medium (Ham F-12 with L-Glutamine)

containing 300 µg/ml G418, 100 U/ml penicillin, 100 µg/ml streptomycin and 10 % inactivated foetal calf serum (FCS).

The cells were seeded at 80'000 cells / well into 96-well black clear bottom sterile plates (Costar) which had been precoated with 1% gelatine in Hanks' Balanced Salt Solution (HBSS). All reagents were from Gibco BRL.

The seeded plates were incubated overnight at 37°C in 5% CO₂.

Human orexin-A as an agonist was prepared as 1 mM stock solution in methanol: water (1:1), diluted in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES for use in the assay at a final concentration of 10 nM.

Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 96-well plates, first in DMSO, then in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES.

On the day of the assay, 100 µl of loading medium (HBSS containing 1% FCS, 2 mM HEPES, 5 mM probenecid (Sigma) and 3 µM of the fluorescent calcium indicator fluo-3 AM (1 mM stock solution in DMSO with 10% pluronic acid) (Molecular Probes) was added to each well.

The 96-well plates were incubated for 60 min at 37° C in 5% CO₂. The loading solution was then aspirated and cells were washed 3 times with 200 µl HBSS containing 2.5 mM probenecid, 0.1% BSA, 2 mM HEPES. 100 µl of that same buffer was left in each well.

Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists were added to the plate in a volume of 50 µl, incubated for 20 min and finally 100 µl of

	<i>IC</i> ₅₀ (nM)	
	<i>OX</i> ₁	<i>OX</i> ₂
Example 3	115	79
Example 7	2400	27
Example 28	153	17
Example 30	261	16
Example 33	127	18
Example 40	37	14
Example 41	52	14
Example 44	67	27
Example 49	12	16
Example 50	14	18
Example 51	28	21

Table 1

agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak induced by 10 nM orexin-A with buffer in place of antagonist. For each antagonist, *IC*₅₀ value (the concentration of compound needed to inhibit 50 % of the agonistic response) was determined. The *IC*₅₀ values of selected compounds are given in Table 1.

II. Chemistry

5 The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof. All temperatures are stated in °C.

All hydrochloride salts were prepared by dissolving the free-base in dichloromethane and treating with an excess of ethereal HCl (2M).

10

A. Abbreviations

15

AIBN 2,2'-azobisisobutyronitrile

BSA Bovine serum albumine

CHO Chinese hamster ovary

DMF Dimethylformamide

20

eq equivalent

ES Electron spray

EtOH Ethanol

FC Flash chromatography

FCS Foetal calf serum

25

FLIPR Fluorescent imaging plate reader

HBSS Hank's balanced salt solution

HEPES 4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid

m multiplet (NMR)

MeCN Acetonitrile

30

MeOH Methanol

MS Mass spectroscopy

NBS *N*-bromosuccinimide

NMR Nuclear magnetic resonance

LC Liquid chromatography

35

q quartet (NMR)

R_t retention time

rt	Room temperature
s	singlet (NMR)
t	triplet (NMR)
TEA	Triethylamine
5 THF	Tetrahydrofuran

B. 2,3-Dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives

10 General procedure:

To a mixture of a 2-aminobenzoic acid derivative (1 g), 2-pyrrolidone (1.5 eq), was added carefully POCl₃ (2.5 mL). The resulting mixture was stirred at 100°C for 1 h under nitrogen. After cooling, the reaction mixture was poured into ice-water, basified with sat.
15 NaHCO₃, extracted with CH₂Cl₂ (3 × 100 mL). The combined extracts were dried (anhydrous MgSO₄), filtered and concentrated to give a crude brown-yellow viscous oil. FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as a solid.

1) 2,3-Dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one

20 FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as a yellow solid (0.97 g, 71%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 2.92 min. *m/z* = 187 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.2 (2H, m), 3.2 (2H, m), 4.2 (2H, m), 7.4 (1H, t), 7.7 (1H, m), 8.3 (1H, d).

25 2) 5-Fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as brown solid (0.92 g, 70%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.21 min. *m/z* = 205 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, q), 3.25 (2H, t), 4.2 (2H, t), 7.4 (2H, m), 8.1 (1H, d).

30

3) 6-Fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as yellow crystals (0.79 g, 60%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.16 min. *m/z* = 206 (M + 2).

¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.15 (1H, m), 7.4 (1H, dd), 8.3 (1H, t).

35

4) 7-Fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one

FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as yellow crystals (0.97 g, 74%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.1 min. *m/z* = 206 (M + 2).

5 ¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, m), 7.7 (1H, m), 7.95 (1H, dd).

5) 6,7-Difluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one

FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as orange crystals (0.86 g, 67%).

10 LC-MS (MeCN/ H₂O: 1/1): R_t = 3.39 min. *m/z* = 224 (M + 2).

¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, t), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, m), 8.00 (1H, m).

6) 6-Chloro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one

15 FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as yellow crystals (1.11 g, 86%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.55 min. *m/z* = 222 (M + 2).

¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, d), 7.6 (1H, s), 8.2 (1H, d).

7) 7-Chloro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one

20 FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as a yellow solid (1.14 g, 89%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.52 min. *m/z* = 222 (M + 2).

¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.6 (2H, q), 8.3 (1H, s).

8) 8-Chloro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one

25 FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as a yellow solid (0.97g, 75%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.30 min. *m/z* = 222 (M + 2).

¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, m), 7.6 (2H, m).

9) **8-Trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

A mixture of 2-amino-6-trifluoromethyl-benzoic acid (0.97 g), 2-methoxypyrroline (0.703 g, 1.5 eq) in dry toluene (12 mL) was stirred at reflux for 3h. The orange solution was then evaporated to dryness to give a crude orange solid

5 FC (CH₂Cl₂/ MeOH: 9/1) afforded the title compound as a yellow powder (0.89g, 74%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.90 min. *m/z* = 255 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.3 (2H, q), 3.2 (2H, t), 4.25 (2H, t), 7.75 (1H, t), 7.85 (2H, d).

10

C. 3-Bromo-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives

General procedure:

15 A mixture of a 2,3-Dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivative (1 eq), NBS (1 eq), AIBN (0.085 eq) in dry CHCl₃ (20 mL/ g) was stirred at reflux for 20 h under nitrogen. After cooling, the mixture was concentrated under reduced pressure, the resulting crude solid was purified by FC (AcOEt/ heptane: 7/3) to give the title compound.

20 1) **3-Bromo-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as brown crystals (40%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.49 min. *m/z* = 266 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.55-2.8 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, m), 7.7 (1H, m), 8.3 (1H, d).

25

2) **3-Bromo-5-fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a n orange solid (35%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.77 min. *m/z* = 285 (M + 2).

¹H-NMR (300MHz; CDCl₃) δ 2.6-2.85 (2H, m), 4.2-4.45 (2H, m), 5.35 (1H, d), 7.5 (2H, m), 8.1 (1H, d).

30

3) **3-Bromo-6-fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a n orange solid (52%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.70 min. *m/z* = 284 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.55-2.8 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.2 (1H, m), 7.5 (1H, m), 8.3 (1H, m).

5 4) **3-Bromo-7-fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a reddish solid (53%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.65 min. *m/z* = 284 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.6-2.85 (2H, m), 4.2-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, m), 7.7 (1H, m), 7.95 (1H, m).

10

5) **3-Bromo-6,7-difluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a red solid (69%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.01 min. *m/z* = 302 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.55-2.8 (2H, m), 4.05-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, m), 8.1 (1H, m).

15

6) **3-Bromo-6-chloro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a reddish solid (42%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.16 min. *m/z* = 300 (M + 1).

20 ¹H-NMR (300MHz; CDCl₃) δ 2.6-2.85 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, dd), 7.7 (1H, s), 8.3 (1H, d).

7) **3-Bromo-7-chloro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a pink solid (49%).

25 LC-MS (MeCN/ H₂O: 1/1): R_t = 4.12 min. *m/z* = 300 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.55-2.85 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.7 (2H, s), 8.3 (1H, s).

8) **3-Bromo-8-chloro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

30 FC (AcOEt/ heptane: 7/3) afforded the title compound as a violet powder (38%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.56 min. *m/z* = 300 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.55-2.85 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, dd), 7.8 (2H, m).

9) **3-Bromo-8-trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**
FC (AcOEt/ heptane: 7/3) afforded the title compound as a red solid (36%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.47 min. *m/z* = 334 (M + 1).

5 ¹H-NMR (300MHz; CDCl₃) δ 2.55-2.85 (2H, m), 4.2-4.5 (2H, m), 5.3 (1H, d), 7.8 (1H, t), 7.9 (2H, m).

C. 3-(1-Phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives

10

General procedure

A mixture of a 3-bromo-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivative (0.56 g, 2.11 mmol), (D,L)-α-methylbenzylamine (1 eq), TEA (1.5 eq) in dry EtOH (10 mL),
15 was stirred at reflux for 20h under nitrogen. After cooling, the reaction mixture was combined with CH₂Cl₂/ water and the aqueous phase was extracted twice with CH₂Cl₂. The combined extracts were dried (anhydrous MgSO₄), filtered and concentrated to give a dark green residue as mixture of diastereoisomers.

20 1) **3-(1-Phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**
FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark green solid (69%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.00 min. *m/z* = 306 (M + 1).

25 2) **6-Fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark oil (56%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.18 min. *m/z* = 324 (M + 1).

30 3) **7-Fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark brown oil (62%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.06 min. *m/z* = 324 (M + 1).

4) **6,7-Difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark green oil (42%).

5 LC-MS (MeCN/ H₂O: 1/1): R_t = 3.31 min. *m/z* = 342 (M + 1).

5) **6-Chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one**

10 FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark green oil (50%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.40 min. *m/z* = 340 (M + 1).

6) **7-Chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one**

15 FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark brown oil (54%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.34 min. *m/z* = 340 (M + 1).

7) **8-Chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one**

20 FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark brown oil (71%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.21 min. *m/z* = 340 (M + 1).

8) **3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one**

25 Reaction with the (S)- α -methylbenzylamine

FC (AcOEt) afforded the title compound as a dark brown oil (68%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.63 min. *m/z* = 374 (M + 1).

9) **5-Fluoro-3-((S)-1-phenyl-ethylamino)-2,3-dihydro-1H-pyrrolo[2,1-*b*]quinazolin-9-one**

30

Reaction with the (S)- α -methylbenzylamine

FC (AcOEt) afforded the title compound as a dark green oil (58%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.36 min. *m/z* = 324 (M + 1).

D. 6,7,8,9-Tetrahydro-pyrido[2,1-*b*]quinazolin-11-one derivatives**General procedure**

5 To a suspension of 2-aminobenzoic acid derivative (1 eq) in dry CHCl_3 (20 mL/ g), was added slowly POCl_3 (1.3 eq) accompanied by stirring for 15 min at rt under nitrogen. Then δ -valerolactam (1.1 eq) was added portionwise over a period of 10 min, the reaction mixture was stirred at reflux under nitrogen for 3 h. Aqueous HCl 5% was added to the reaction mixture, the aqueous phase was separated (this operation was repeated three
10 times). The combined aqueous extracts were clarified by adding active charcoal and filtered through celite. The resulting pale yellow solution was basified with concentrated aqueous ammoniac and extracted with CH_2Cl_2 (three times). The combined organic extracts were washed with water, dried (anhydrous Na_2SO_4), concentrated under reduced pressure to give a solid which was used for the next step without further purification.

15

1) 6,7,8,9-Tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Light orange crystals (41%)

LC-MS (MeCN/ H_2O : 1/1): R_t = 2.83 min. m/z = 201 ($M + 1$).

$^1\text{H-NMR}$ (300MHz; CDCl_3) δ 2.00 (4H, m), 3.1 (2H, t), 4.1 (2H, t), 7.5 (1H, t), 7.6-7.8
20 (2H, m), 8.3 (1H, d).

2) 3-fluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow crystals (44%)

LC-MS (MeCN/ H_2O : 1/1): R_t = 3.34 min. m/z = 219 ($M + 1$).

$^1\text{H-NMR}$ (300MHz; CDCl_3) δ 2.00 (4H, m), 3.0 (2H, t), 4.1 (2H, t), 7.1 (1H, m), 7.2 (1H,
25 d), 8.3 (1H, t).

3) 2-fluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (56%)

30 LC-MS (MeCN/ H_2O : 1/1): R_t = 3.39 min. m/z = 219 ($M + 1$).

$^1\text{H-NMR}$ (300MHz; CDCl_3) δ 2.00 (4H, m), 3.0 (2H, t), 4.1 (2H, t), 7.4 (1H, m), 7.6 (1H,
m), 7.9 (1H, dd).

4) 2,3-Difluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow crystals (45%)

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.82 min. *m/z* = 237 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.00 (4H, m), 2.95 (2H, t), 4.1 (2H, t), 7.35 (1H, q), 8.0 (1H, t).

5

E. 6-Bromo-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one derivatives

These compounds have been prepared as described for the 3-bromo-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives.

10

1) 6-Bromo-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Pale yellow crystals (55%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.86 min. *m/z* = 280 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.1-2.6 (4H, m), 4.00 (1H, m), 4.4 (1H, m), 5.4 (1H, s), 7.5 (1H, t), 7.7 (2H, m), 8.3 (1H, d).

15

2) 6-Bromo-3-fluoro-6,7,8,9-Tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Pale yellow crystals (65%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.21 min. *m/z* = 298 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.1-2.6 (4H, m), 4.00 (1H, m), 4.4 (1H, m), 5.4 (1H, s), 7.2-7.5 (2H, m), 8.3 (1H, d).

20

3) 6-Bromo-2-fluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

White solid (69%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.20 min. *m/z* = 298 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.1-2.6 (4H, m), 4.00 (1H, m), 4.4 (1H, m), 5.35 (1H, s), 7.5 (1H, m), 7.7 (1H, m), 7.9 (1H, dd).

25

4) 6-Bromo-2,3-difluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

White solid (55%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.49 min. *m/z* = 316 (M + 1).

¹H-NMR (300MHz; CDCl₃) δ 2.1-2.6 (4H, m), 3.95 (1H, m), 4.4 (1H, m), 5.35 (1H, s), 7.45 (1H, t), 8.05 (1H, t).

30

F. 6-(1-Phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one derivatives

These compounds have been prepared as described for the 3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives (mixture of diastereoisomers).

1) 6-(1-Phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Pale yellow solid (72%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 2.98 and 3.19 min. *m/z* = 320 (M + 1).

2) 3-Fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (40%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.18 min. *m/z* = 338 (M + 1).

3) 2-Fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (26%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.14 min. *m/z* = 338 (M + 1).

4) 2,3-Difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (40%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 3.15 min. *m/z* = 356 (M + 1).

Example 1

1-(9-Oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diastereoisomers)

To a solution of 3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (50 mg, 0.163 mmol) in dry CH₂Cl₂ (1 mL), was added 2-n-propylphenyl isocyanate (26.3 mg, 0.163 mmol). The resulting reaction mixture was stirred at rt under nitrogen for 20h. The reaction mixture was then concentrated under reduced pressure and the residue was

purified by FC (AcOEt/ heptane: 7/3) to give the title compound as a white foam (45%).
LC-MS (MeCN/ H₂O: 1/1): R_t = 3.00 min. *m/z* = 467 (M + 1).

Example 2

5

3-Biphenyl-2-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using with 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (63%).

10 LC-MS (MeCN/ H₂O: 1/1): R_t = 4.89 and 5.49 min. *m/z* = 500 (M).

Example 3

15

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 2-ethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (55%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.60 and 5.23 min. *m/z* = 468 (M).

20

Example 4

25

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (62%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.76 and 5.33 min. *m/z* = 470 (M).

30

Example 5

35

3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (82%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.01 and 5.61 min. *m/z* = 518 (M).

Example 6

5

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-*n*-propylphenyl isocyanate

10 (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige powder (61%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.06 and 5.61 min. *m/z* = 484 (M).

Example 7

15

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

20 FC (AcOEt/ heptane: 7/3) afforded the title compound as a white solid (72%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.92 and 5.61 min. *m/z* = 526 (M).

Example 8

25 **1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)**

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-isopropylphenyl isocyanate (1 eq).

30 FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (70%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.98 and 5.48 min. *m/z* = 484 (M).

Example 9

5 **1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea (mixture of diastereoisomers)**

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 1-naphthyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown oil (77%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.72 and 5.28 min. *m/z* = 492 (M).

10

Example 10

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-propyl-phenyl)-urea (mixture of diastereoisomers)

15 In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-*n*-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as an orange oil (75%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.99 and 5.53 min. *m/z* = 484 (M).

20

Example 11

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diastereoisomers)

25 In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown oil (83%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.85 and 5.52 min. *m/z* = 526 (M + 1).

30 **Example 12**

3-Biphenyl-2-yl-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow brown oil (70%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.02 and 5.59 min. *m/z* = 518 (M).

5

Example 13

3-(2-Ethyl-phenyl)-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

10 In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (70%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.77 and 5.32 min. *m/z* = 470 (M).

15 Example 14

3-Biphenyl-2-yl-1-(6,7-difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

20 In analogy to Example 1 using 6,7-difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale grey foam (56%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.27 and 5.84 min. *m/z* = 536 (M).

Example 15

25

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6,7-difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

30 FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown foam (61%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.07 and 5.74 min. *m/z* = 544 (M).

Example 16

5 **1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diastereoisomers)**

In analogy to Example 1 using 6,7-difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown foam (67%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.22 and 5.74 min. *m/z* = 502 (M).

10

Example 17

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

15 In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale beige foam (66%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.09 and 5.73 min. *m/z* = 487 (M).

20 **Example 18**

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 1-naphthyl isocyanate (1 eq).

25 FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige solid (47%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.99 and 5.61 min. *m/z* = 509 (M).

Example 19

30

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-isopropylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a grey solid (87%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.30 and 5.81 min. *m/z* = 501 (M).

5

Example 20

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea (mixture of diastereoisomers)

10 In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-*n*-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (58%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.34 and 5.92 min. *m/z* = 501(M).

15 Example 21

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diastereoisomers)

20 In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale brown foam (74%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.18 and 5.92 min. *m/z* = 542 (M).

Example 22

25

3-Biphenyl-2-yl-1-(7-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenyl isocyanate (1 eq).

30 FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (72%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.36 and 5.99 min. *m/z* = 535 (M).

Example 23

3-Biphenyl-2-yl-1-(11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-b]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-b]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow oil (22%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.99 and 5.80 min. *m/z* = 515 (M + 1).

10

Example 24

1-(11-Oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-b]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-b]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (53%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.18 and 5.86 min. *m/z* = 481 (M + 1).

20 **Example 25**

3-(2-Ethyl-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-b]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-b]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

25

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow oil (72%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.87 and 5.54 min. *m/z* = 467 (M + 1).

Example 26

30

3-(2-Ethoxy-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-b]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige solid (41%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.81 and 5.67 min. *m/z* = 483 (M + 1).

5

Example 27

3-Naphthalen-1-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

10 In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 1-naphthyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige solid (28%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.87 and 5.51 min. *m/z* = 489 (M + 1).

15 **Example 28**

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diastereoisomers)

20 In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (80%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 6.13 min. *m/z* = 517 (M + 1).

Example 29

25

3-Biphenyl-2-yl-1-(2,3-difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).

30 FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (48%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.57 and 6.22 min. *m/z* = 551 (M + 1).

Example 30

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

- 5 In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (97%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.35 and 5.92 min. *m/z* = 503 (M + 1).

10 **Example 31**

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

- 15 In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (60%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.22 and 6.07 min. *m/z* = 519 (M + 1).

Example 32

20

3-Biphenyl-2-yl-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).

- 25 FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (42%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.38 and 6.10 min. *m/z* = 533 (M + 1).

Example 33

- 30 **1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diastereoisomers)**

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (98%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.29 and 5.96 min. *m/z* = 499 (M + 1).

Example 34

5

3-(2-Ethoxy-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).

10

FC (AcOEt/ heptane: 7/3) afforded the title compound as a foam (88%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.03 and 5.93 min. *m/z* = 501 (M + 1).

Example 35

15

3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a foam (47%).

20

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.07 and 5.74 min. *m/z* = 485 (M + 1).

Example 36

25

3-Biphenyl-2-yl-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow powder (43%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.38 and 6.07 min. *m/z* = 533 (M + 1).

Example 37

5 **1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diastereoisomers)**

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as an orange-brown powder (53%).

10 LC-MS (MeCN/ H₂O: 1/1): R_t = 5.29 and 5.94 min. *m/z* = 499 (M + 1).

Example 38

3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-
15 *b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow powder (44%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.03 and 5.86 min. *m/z* = 501 (M + 1).

20

Example 39

3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-
25 *b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow powder (54%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.07 and 5.72 min. *m/z* = 485 (M + 1).

30 **Example 40**

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-
3-(2-trifluoromethoxy-phenyl)-urea (mixture of diastereoisomers)

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq). FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (74%). LC-MS (MeCN/ H₂O: 1/1): R_t = 4.97 and 5.74 min. *m/z* = 542 (M).

5

Example 41**3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)**

10 In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq). FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow foam (70%). LC-MS (MeCN/ H₂O: 1/1): R_t = 5.16 and 5.80 min. *m/z* = 535 (M).

15 **Example 42****1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropylphenyl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)**

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-isopropylphenyl isocyanate
20 (1 eq). FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (70%). LC-MS (MeCN/ H₂O: 1/1): R_t = 5.11 and 5.67 min. *m/z* = 501 (M).

25 **Example 43****1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)**

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 1-naphthyl isocyanate (1 eq).
30 FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (57%). LC-MS (MeCN/ H₂O: 1/1): R_t = 4.83 and 5.46 min. *m/z* = 509 (M).

Example 44

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea (mixture of diastereoisomers)

- 5 In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-*n*-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (64%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.11 and 5.74 min. *m/z* = 501(M).

10 **Example 45**

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diastereoisomers)

- In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-
15 pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale beige foam (83%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 4.86 and 5.53 min. *m/z* = 486 (M).

Example 46

20

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea

In analogy to Example 1 using 5-fluoro-3-((S)-1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-*n*-propylphenyl isocyanate (1 eq).

- 25 FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale beige foam (57%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.27 and 5.74 min. *m/z* = 485 (M + 1).

Example 47

- 30 **3-Biphenyl-2-yl-1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea**

In analogy to Example 1 using 5-fluoro-3-((S)-1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a green foam (73%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.39 and 5.94 min. *m/z* = 519 (M + 1).

Example 48

5

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea

In analogy to Example 1 using 5-fluoro-3-((S)-1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

10 FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale green solid (62%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.13 and 5.72 min. *m/z* = 527 (M + 1).

Example 49

15 **1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea**

In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

20 FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (68%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.39 and 6.14 min. *m/z* = 577 (M + 1).

Example 50

25 **1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea**

In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-*n*-propylphenyl isocyanate (1 eq).

30 FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (54%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.54 and 6.13 min. *m/z* = 535 (M + 1).

Example 51**3-(2-Ethyl-phenyl)-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-
5 b]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea**

In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (62%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.34 and 5.96 min. *m/z* = 521 (M + 1).

10

Example 52**3-Biphenyl-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-
yl)-1-((S)-1-phenyl-ethyl)-urea**

15 In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (72%).

LC-MS (MeCN/ H₂O: 1/1): R_t = 5.64 and 6.22 min. *m/z* = 569 (M + 1).

20

25

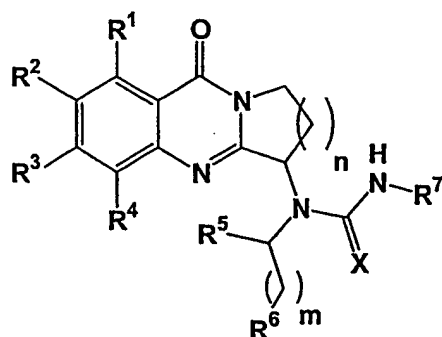
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Claims

1. Compounds of the general formula (I)

5



formula (I)

10

wherein:

X is O or S;

n is the integer 1, 2, or 3;

15 m is the integer 0, 1, 2, 3;

R¹, R², R³, R⁴ independently represent cyano, nitro, halogen, hydrogen,

hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl,

trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy,

heterocyclylalkyloxy, R⁸CO-, N R⁹R¹⁰CO-, R⁹R¹⁰N-, R⁸OOC-, R⁸SO₂NH-,

20 R¹¹-CO-NH- or R² and R³ together or R¹ and R² together or R³ and R⁴ together

may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom.

R⁵ represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

25 R⁶ represents hydrogen, lower alkyl, trifluoromethyl, -(CH₂)_m-OH, -(CH₂)_m-O-lower alkyl, -(CH₂)_m-CO₂H, -(CH₂)_m-CO₂-lower alkyl, -(CH₂)_mCONH₂, -(CH₂)_m-CONH-lower alkyl, or -(CH₂)_m-CON-(lower alkyl)₂, or -(CH₂)_m-N-(lower alkyl)₂;

R⁷ represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R⁸ represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R⁹ and R¹⁰ independently represent hydrogen, alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R¹¹ represents lower alkyl, aryl, cycloalkyl, heterocyclyl, R⁹R¹⁰N- or R⁸O-.

5 and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula I, wherein n is the integer 1 or 2, m is the integer 0, 1 or 2, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ have the meaning given in the formula I above and X
10 represents oxygen.

3. Compounds of the general formula I wherein n is the integer 1 or 2, m is the integer 0, R⁵ represents methyl, R⁶ represents phenyl, R¹, R², R³, R⁴, and R⁷ have the meaning given in the formula I above and X represents oxygen.

4. A compound according to any one of claims 1 to 3, selected from the group consisting of
15 1-(9-Oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-Biphenyl-2-yl-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
20

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-Naphthalen-1-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
25

3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-propyl-phenyl)-urea;
30

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

- 1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;
- 5 1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
- 3-Biphenyl-2-yl-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 10 3-(2-Ethyl-phenyl)-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(6-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 15 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;
- 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 20 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
- 25 3-Biphenyl-2-yl-1-(7-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;
- 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 30 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

- 3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 5 1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;
- 3-Biphenyl-2-yl-1-(6,7-difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;
- 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-
- 10 (2-trifluoromethoxy-phenyl)-urea;
- 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
- 15 3-Biphenyl-2-yl-1-butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;
- 1-Butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-*n*-propyl-phenyl)-urea;
- 1-Benzyl-3-biphenyl-2-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;
- 1-Benzyl-3-(2-ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-
- 20 urea;
- 1-Benzyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-*n*-propyl-phenyl)-urea;
- 3-Biphenyl-2-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 25 1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 3-(2-Ethyl-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 3-(2-Ethoxy-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 30 3-Naphthalen-1-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

- 3-Biphenyl-2-yl-1-(2,3-difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 5 1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;
1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea;
- 10 3-Biphenyl-2-yl-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
3-(2-Ethoxy-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 15 3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 20 1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
- 25 3-Biphenyl-2-yl-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;
1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7H-pyrido[2,1-*b*]quinazolin-6-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;
1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((*S*)-1-phenyl-ethyl)-
- 30 3-(2-*n*-propyl-phenyl)-urea;
3-Biphenyl-2-yl-1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((*S*)-1-phenyl-ethyl)-urea;

- 1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
- 1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;
- 5 1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-urea;
- 3-(2-Ethyl-phenyl)-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea;
- 3-Biphenyl-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea.
- 10

5. Pharmaceutical compositions for the treatment of disorders which are associated with the role of orexin, especially disorders such as obesity and sleep disorders, containing one or more compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.
- 15 6. The compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use as medicaments for the treatment of disorders which are associated with a role of orexin, especially obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders.
- 20 7. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.
8. A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with the role of orexin, especially obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders, containing one or more compounds as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt or salts thereof, as active ingredients which process comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.
- 25 30 9. Use of one or more compounds of any one of claims 1 to 4 in combination with other pharmacologically active compounds comprising other orexin receptor antagonists, lipid lowering agents, anorectic agents, sleep inducing agents, antidepressants or other drugs

beneficial for the prevention or treatment of disorders given in any one of claims 6 to 8.

10. A compound as described as end-product in any one of examples 1 to 63.

11. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/EP 03/07297

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/519 C07D487/04 C07D471/04 A61P3/04 A61P25/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 47580 A (COULTON STEVEN ;JOHNS AMANDA (GB); PORTER RODERICK ALAN (GB); SMIT) 17 August 2000 (2000-08-17) cited in the application the whole document -----	1-10

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

23 September 2003

Date of mailing of the international search report

02/10/2003

Name and mailing address of the ISA

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Authorized officer

Schmid, J-C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07297

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 11

Present claim 11 is not clear in scope that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely claims 1-10.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07297

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0047580	A	17-08-2000	AU 2910600 A	29-08-2000
			WO 0047580 A2	17-08-2000
			EP 1144409 A2	17-10-2001
			JP 2002536447 T	29-10-2002
			US 6596730 B1	22-07-2003